Introduction

Over the past 20 years, there has been a shift in head and neck cancer. Oropharyngeal squamous cell carcinoma has overtaken laryngeal squamous cell carcinoma as the most common form of head and neck cancer. Most interestingly, an ever-growing subpopulation of oropharyngeal squamous cell carcinoma has become ever more prevalent over this time period. The discovery of the relationship between the Human Papilloma Virus (HPV) and oropharyngeal squamous cell carcinoma has led to numerous findings including improved outcomes and response to therapies. What once was known a chemical carcinogen-induced disease, centers are seeing large numbers of HPV-induced tumors (Haughey and Sinha).

Treatment of Oropharyngeal SCCA (OPSCC) has evolved over the last half century. What was once a primarily surgical disease, often with concomitant morbidity and mortality, oropharyngeal squamous cell carcinoma began to be treated with “organ-preservation” chemotherapy and radiation with improved morbidity and mortality. However, the advances in transoral laser microsurgery and, more recently, transoral robotic surgery or TORS have led surgeons to revisit the surgical and nonsurgical approach in oropharyngeal SCCA. TORS, in particular, has garnered much attention. Research directed at the efficacy of surgically treated oropharyngeal squamous cell carcinoma has been prolific in Otolaryngology literature.

Human Papillomavirus

First discovered around 25 years ago, the association between the Human Papilloma Virus and Oropharyngeal SCCA had led to a greater understanding in the difference of outcomes in patients with oropharyngeal squamous cell carcinoma. There are several unique characteristics of the HPV virus that predicate the development of squamous cell carcinoma. The Human Papillomavirus (HPV) is a double-stranded circular DNA virus made of a single DNA molecule surrounded by a capsid. The genome for the HPV virus is divided into an early region and a late region. The papillomavirus replicates exclusively in keratinocytes, and generally small cuts or wounds in the skin or mucosa allow the virus access to the basal stem cells. Viral proteins E1 and E2 maintain viral DNA as a circular episome. E6 and E7 are very
important viral oncogenes which promote cell growth by inactivation of tumor suppressor proteins p53 and pRb. There are more than 118 HPV's described. The two major groups are low risk (HPV 6 and 11) and high-risk (HPV 16 and 18). HPV 16 and 18 predominate in cervical and head and neck cancers.

It is believed that malignant transformation from HPV is related to two central components: 1) inactivation of the cellular p53 gene by E6, 2) inactivation of the cellular pRb gene by HPV E7. HPV appears to target the same molecular pathways as the mutagens present in tobacco and alcohol. However, studies have shown that the possible improved prognosis is patients with HPV-related SCCA merely have an inactivation of p53 while those cancers related to tobacco and alcohol have a mutation and loss of p53 (Haughey and Sinha). Carcinogenesis in HPV-positive OPSCC is a process of cell cycle deregulation mediated by viral oncoproteins, which is specific to the epithelium under transformation. The highly localized carcinogenesis in HPV-positive OPSCC represents a profound difference in tumor biology. (Bonilla-Velez, Mroz and Hammon) HPV-16 causes 90% of HPV-positive OPSCC. The prevalence of oral HPV-16 infection is 1% in the United States and has been associated with a 50-fold increased risk for HPV-positive OPSCC. (Bonilla-Velez, Mroz and Hammon) Gillison et al. reviewed HPV-positive OPSCC and found patient with 26 or more vaginal sex partners or 6 or more oral sex partners had a dramatically increased risk with odds-ratio of 3.1 and 3.4 respectively. (de Almeida and Genden) The differing phenotypic and biological profile of the HPV-associated OPSCC leads to superior disease-free and overall survival outcomes. Bledsoe et al reviewed their experience with HPV-positive OPSCC versus HPV-negative OPSCC and found statistically significant improvement in overall survival and locoregional recurrence rates. Overall survival was 94% in the HPV-positive OPSCC patients versus 73% in the HPV-negative OPSCC. (Bledsoe, Noble and Hunter) Multiple studies have shown the survival benefit comparing HPV-positive OPSCC to HPV-negative OPSCC.

Ang et al. reviewed and analyzed RTOG 0129 which was looking at accelerated versus standard fractionation radiation therapy with concurrent cisplatin to look at trends due to HPV status. In comparing the two groups, overall survival in HPV-positive patients at 3 years was 82% while overall survival in HPV-negative patients was 57.1% at 3 years. Progression-free survival in HPV(+) patients was 73.7% versus 43.4% in HPV-negative patients. Locoregional recurrence in HPV-positive patients was 13.6% versus 35.5% in HPV-negative patients. (Bonilla-Velez, Mroz and Hammon) Multiple other studies which have compared the two groups have noted an improved survival benefit due to HPV-positive OPSCC.

**Current Treatment**

Current treatment for oropharyngeal squamous cell carcinoma is based on staging. Early-stage OPSCC can generally be treated with radiation therapy alone. However, late-stage OPSCC will generally require a combination of chemotherapy and radiation therapy. The current guidelines recommend a standard therapy with once daily XRT in fractions of 2 Gy/fraction for a total dose of 70-74 Gy. This is over a 6 week period. Concurrent chemotherapy involves single agent high-dose Cisplatin of 100mg/m2 in 3 doses over the course of the treatment. In the past, patients with neck disease would undergo post-treatment neck dissection prophylactically. However, review of the pathology revealed a less than 10% occurrence of pathologically-positive persistent neck disease. Currently, salvage neck dissections are reserved for PET(+) lymph nodes 3 months after concurrent treatment or for clinically-concerning neck masses.
The known toxicities and side effects of radiation and chemotherapy are loss of taste, xerostomia, need for feeding tube/dysphagia, febrile neutropenia, radiation dermatitis, and pain. Machtay et al. reviewed the analysis of three separate RTOG trials. They found that the rate of severe late toxicities was 43% for all patients treated with 35% in patients treated for oropharyngeal carcinoma. Late toxicities were defined as grade 3 or 4 laryngeal toxicity, feeding tube dependence at 2 years and beyond, and/or treatment-related deaths. In reviewing their literature, Bledsoe et al. looked at comparing toxicities between HPV-positive and HPV-negative OPSCC. The acute toxicities were very comparable with similar rates for need for feeding tube, febrile neutropenia, radiation dermatitis, pain during treatment, and pain at 90 days. When reviewing late toxicities, after 6 months, the need for feeding tube rate was 0% in HPV-positive patients versus 24% in HPV-negative patients. Also, the rate of trismus was significantly improved with a rate of 1% versus 24%. Rates of xerostomia and dysphagia were comparable. (Bledsoe, Noble and Hunter) The changing epidemiology associated now with HPV-positive OPSCC has led to a younger patient population. With this younger population, late toxicities and side effects from chemoradiotherapy can have longer impacts of quality of life. The introduction of trans-oral robotic surgery has brought in new innovation in the treatment of oropharyngeal carcinomas.

**Robotic Surgery**

In 1985, the Puma 560 was introduced to help surgeons perform more precise neurosurgical biopsies. 3 years after the introduction, the robot was used to perform trans-urethral resection of the prostate. With the hope that surgeons could be placed away from battle action but perform surgery, “telepresence” surgery was aided both by the US Army and NASA. This has been successful but limited by the ability of available high-speed intranet. NASA had hoped to develop a way to perform surgical intervention in space from a remote location. The FDA had since begun to approve robotic surgery in multiple fields, and, in 2009, the FDA approved the use of the robot in transoral robotic surgery. (de Almeida and Genden) The first preclinical studies were performed at the University of Pennsylvania. O’Malley et al first described their experience with trans-oral robotic surgery (TORS) tongue base resections. (O’Malley BW) With the experience from Drs. Laccoureye and Holsinger who described a case series of tonsillar SCC treated with transoral lateral pharyngotomy, minimally invasive techniques were conceived using the robot.

Subsequently, the University of Pennsylvania reported the first case series of TORS cases for radical tonsillectomy with an n of 27 patients. Their surgical complication rate was 19% with one mucosal hemorrhage requiring return to the OR, one tracheostomy for OSA exacerbation, 2 patients who developed trismus, and 1 patient who developed hypernasality. Genden et al. from the Mount Sinai group then reported their experience with 20 patients. Genden’s data revealed patients returning to oral diet on an average of 1.4 days after surgery. Only 2 of their cases were aborted secondary to inadequate exposure. (de Almeida and Genden) These studies were able to prove the feasibility and safety of TORS. They have since laid the foundation for further study.

The general set-up of transoral robotic surgery includes the robot, generally placed at a 45 degree angle to the left of the head of the patient’s bed. The patient, depending upon the surgical approach is intubated with a nasotracheal tube. The anesthesia team is often set-up 90 degrees to the right of the patient, or, in some cases, 180 degrees at the foot of the patient. The scrub nurse is placed to the right or
Transoral Robotic Surgery (TORS) and HPV (+) Oropharyngeal Surgery

September 2013

left of the head of the bed while the assistant surgeon sits at the head of the bed. The primary surgeon then
sits at the console. The da Vinci system is set-up where a slave monitor is placed for the use by the
assistant surgeon and scrub tech. A speaker system allows for clear communication from the primary
surgeon to the team. The assistant surgeon works to keep the camera clean, smoke out of the surgical field,
and assist with cautery as needed. There are multiple mouth gags available for use including the Macgyver
and Crow-Davis. The Feyh-Kastenbauer or FK retractor has become very popular. It has multiple points
of rotation for different ways to suspend the patient. This allows for different aspects of exposure. These
multiple points of rotation are especially helpful in base of tongue masses. The camera source is brought in
to the midline of the mouth. The two working arms are set at roughly 30-45 degree angles to the right and
left of the camera allowing for maximal freedom of movement without hitting the camera or the other
working arm. Once must take special care at the molar teeth. A distinct disadvantage of the robot is a lack
of tactile feedback.

Radical tonsillectomy is generally performed using a bovie cautery and a Maryland retractor.
Mucosal incisions are made along the tonsillar fossa in the same manner as a standard tonsillectomy. Once
deep to the superficial layers, the palatopharyngeus, palatoglossus and superior constrictor muscles are
identified. The muscles are then transected and the tumor is retracted medially. The parapharyngeal fat is
often exposed at this point. Deep to the parapharyngeal fat is the carotid artery. During the dissection, two
large arteries are often identified. Those are the ascending palatine and ascending pharyngeal artery.
These arteries should be ligated with vascular clamps. Dissection is then brought inferiorly toward the
base of tongue where the styloglossus muscle is often identified. The glossopharyngeal nerve can be
identified at this time. The inferior cuts are then made and the tumor is retracted further medially and taken
off the posterior pharyngeal mucosa. (Gross)

**Tumor Margins**

One of the most important aspects of surgical oncology is the ability to get a safe and reliable
negative margin. Haughey et al noted a presence of positive margins after surgery raises the risk of death
in patients 2.5-3.0 fold. Checking tumor margins in TORS can be challenged and requires a collaborative
approach between the surgeon and the pathologist. The University of Pennsylvania group has detailed their
experience with checking tumor margins. The surgeon delivers the specimen to pathology lab and will ink
the specimen with various permanent inks to denote pertinent margins. The specimen is then pinned to the
cork board for proper orientation. After review of the specimen, if gross margins are suspected, the
surgeon may perform a second margin. The pathologist may also perform frozen sections. After re-
section, the operative bed is stained with methylene blue to ensure proper orientation if any more sections
are required. (Weinstein, O'Malley and Quon, Transoral Robotic Surgery for Advanced Oropharyngeal
Carcinoma)

**Squamous Cell Carcinoma of Unknown Primary Tumors**

The advent and use of transoral robotic surgery has also led to the use in patients with unknown
primary tumors. Patients who are diagnosed with an unknown primary tumor have been found to have
significantly lower survival compared to those with a known primary tumor. This leads to wide field
treatment of the entire upper aerodigestive tract. The 5-year actuarial survival rate for patients with N1,
N2, and N3 disease with an unknown primary is 69%, 58% and 30% respectively. Mehta et al. began to
perform base of tongue carpet resections to help in diagnosis of patient’s with unknown primary tumors. They reviewed 10 patients who had previously undergone panendoscopy with directed biopsies, PET/CT imaging, and bilateral tonsillectomy. In each of these patients, a primary tumor was not found. The patients then underwent base of tongue carpet resection using TORS. In 9 of the 10 patients, a squamous cell carcinoma was identified while 1 patient did not have a primary site identified. The identification of the primary mucosal lesion leads to a vast improvement in 5 year survival while incurring a potential reduction in morbidity by reducing radiation toxicity to other pharyngeal subsites. (Mehta, Johnson and Tassler)

**Outcomes of TORS**

Weinstein et al. reported the first prospective trial of TORS from the University of Pennsylvania in 2010. The group pooled data collected from 162 patients. Patient underwent Transoral robotic surgery followed by staged neck dissection 3 weeks after resection. The group felt that staging the neck dissections would avoid creating connection between the neck and pharynx and avoid additional laryngopharyngeal swelling. Each patient underwent a selective neck dissection of levels I-III or IV.

Adjuvant therapy was offered to patients based upon prior surgical guidelines. These include questionable surgical margins and presence of 2 or more pathologically positive lymph nodes. These patients were given post-operative radiation. Relative indications for post-operative radiation included T4 disease with an infiltrative growth pattern, presence of perineural invasion, and the presence of 1 pathological lymph node. Patients who received adjuvant chemotherapy and radiation were included based on prior findings from Bernier et al. recommendations. These included positive surgical margins, extracapsular extension, and multiple lymph nodes without ECE.

A total of 47 primary TORS procedures were performed with a minimum of 18 months follow-up. There was no mention of HPV status in their study. 1 patient (2%) had a positive histologic margin. Local disease control in the patients was 98%. 96% of the patients had regional control. 91% of the patients had distant control. In review of their patients, 38% of the patients with stage III and IV pts avoided chemotherapy. The overall survival rate for the patients was 96% at 1 year and 82% at 2 years. Disease-specific survival was 98% at 1 year and 90% at 2 years. Disease-free survival was 96% at 1 year and 79% at 2 years. (Weinstein, O'Malley and Quon, Transoral Robotic Surgery for Advanced Oropharyngeal Carcinoma)

Moore et al reviewed their experience at Mount Sinai from 2007 and 2009 to evaluate functional and oncologic results utilizing TORS. In comparison to the previous study, the patients in this study were tested for HPV status. Of the 66 patients, 58 patients were positive for p16 (89.2%). 56 of the 66 patients presented with a clinical stage T1 or T2. Lymph node metastases were noted in 86.4% of the patients after pathologic staging. In the end, the overall stage of the patients was III-IVb in 87.9% of the patients. Each patient underwent primary tumor resection with TORS. Only 54.5% (36 pts) of patients had a clear margin after initial resection. 12 patients (18.2%) of patients required a second margin excision and 18 (27.3%) patients required 3 or more margin excisions on the initial operation. 1 specimen was noted to have positive margin on final histologic review.
As opposed to the UPENN group, Moore et al. performed neck dissections in each of the patients at the same time as the TORS procedure. 56 (84.8%) patients underwent unilateral neck dissection while 10 (15.2%) patients underwent bilateral neck dissection.

Reviewing their outcomes, the group found that tumor depth varied from 4-10 mm and greater than 10 mm in 80.3% of the patients. The majority of the patients (87.9%) did not have angiolymphatic invasion. Only 6 patients demonstrated bilateral lymph node metastases. Extracapsular spread (ECS) was found in 56.1% of patients. Reviewing disease-specific 3-year survival and recurrence-free 3-year survival, tobacco use was not a significant factor. HPV status was an important factor in both survival curves. Disease-specific 3-year survival was 97.8% versus 88.9% in HPV-negative patients.

Recurrence-free 3-year survival in HPV-positive patients was 96% versus 83.3% in HPV-negative patients. Both of these data sets were found to be statistically significant. When comparing HPV-status and tobacco abuse, however; there was no significant difference in survival based on tobacco abuse. There did appear to be a downward trend in survival among HPV-positive smokers. Moore et al. found that margin control was a very important prognostic factor in their patients, and they found that only 54% of patients had clear margins after the initial resection. In review of the data, Moore et al. recommended further studies to investigate de-escalation trials in subsets of patients with a favorable prognosis. (Moore, Henstrom and Olsen)

In order to understand the local control of TORS surgery, Weinstein et al. performed a review of their TORS experience and evaluated patients who underwent TORS +/- selective neck dissection without adjuvant therapy. They found 30 patients with a minimum follow-up of 18 months. 3 patients had perineural invasion, and 1 patient had lymphovascular invasion. 16 patients were initially a stage III/IV prior to surgical treatment. In this patient group, only 1 patient had a local recurrence. Unfortunately, there was no HPV or p16 analysis in these patients. Weinstein et al. theorized that the HPV numbers would be high and cited a study by Cohen et al that found 74% of their patients were HPV-positive (Cohen, Weinstein and O’Malley). Weinstein et al. were able to prove the efficacy of TORS in local control of oropharyngeal carcinomas.

With the improved outcomes noted in TORS, Weinstein et al wanted to then assess whether de-intensifying treatment would lead to similar or improved outcomes. The indications for patients would be based on pathologic status of lymph nodes.

The patients underwent selective neck dissection with levels I-IV. There were 32 patients between 2005 and 2007. The primary outcome of the study was to measure regional recurrence rate. Each patient had a minimum post-operative follow-up of 18 months. Contraindications for selective neck dissection in the patient population including stage IVc disease, carotid artery encasement, deep neck structure involvement, skin invasion with dermal metastasis, invasion of the sternocleidomastoid muscle, invasion of cranial nerve XI, or invasion of the internal jugular vein.

29 patients underwent ipsilateral neck dissection, while 2 patients underwent bilateral selective neck dissection. Clinical N0 and N1 neck disease were upstaged 33% and 43% respectively on pathology. Only 29% of the patients in this study were found to have extracapsular extension (ECE) on pathology; however,
70% of patients with N2b disease had ECE. Only 14% of patients with N1 disease had ECE. 4 of 14 (29%) patients with clinical N1 disease had negative pathology after surgery. Adjuvant chemoradiation was indicated if the patient had positive surgical margins or the presence of ECE. In their cohort, 22.6% of patients received no adjuvant therapy.

24 patients received adjuvant treatment. Of the 24 patients, 50% received adjuvant radiation while 50% received adjuvant chemoradiation. There was only 1 regional recurrence, 1 local recurrence, and 1 distant recurrence in their study. The study found a control rate of 100% after selective neck dissection. ECE was only found in 29% of the patient while pathological N2b disease was found in 61% of patients. The study concluded that selected patients with clinical low risk N0 and N1 disease could possibly be observed. They found that the risk of recurrence was less than 5% in patients with pathologic N1 disease and lymph nodes less than 3 cm. (Weinstein, Quon and O'Malley)

In 2010, Cohen et al reviewed their experience with TORS and HPV-related OPSCC. The group looked at a cohort of 50 patients diagnosed with OPSCC. They found 37 patients were HPV-positive while 13 patients were HPV-negative. 76.9% of their HPV-negative patients were either Stage III or Stage IV. 91.9% of their HPV-positive patients were Stage III or Stage IV. In comparing the role of adjuvant treatment, they found that 56.8% of patients with HPV-positive OPSCC received adjuvant chemotherapy and radiation. 27% of the patients received radiation only. 5.4% of the patients received chemotherapy alone, while 10.8% of their patients did not receive any adjuvant treatment. In the HPV-negative OPSCC patients, 46.2% of patients received adjuvant chemotherapy and radiation. 38.5% of their patients did not require adjuvant therapy.

Cohen et al then examined the results of neck dissections in their patients. They found that in HPV-positive patients, 30 of 36 or 83.3% of patients had pathological positive nodal disease. In HPV-negative patients, 9 of 12 had pathological positive nodal disease. They performed Kaplan Meier survival curves comparing HPV-positive and HPV-negative patients observing overall survival (OS), disease-specific survival (DSS) and disease-free survival (DFS). HPV-positive OPSCC showed a statistical improvement in overall survival and disease-free survival. Their study failed to show a statistical difference in disease-specific survival. The study was able to prove the effectiveness of TORS in patients with HPV(+) disease compared to those with HPV-negative disease. (Cohen, Weinstein and O'Malley) While the effectiveness of TORS in HPV-negative patients was proven, there was some concern in evaluating patient outcomes with HPV-positive disease. Their study was published in 2012 and was based on trans-laser microsurgery instead of trans-oral robotic surgery. They performed a prospective study in patients with diffusely positive p16 on IHC. The patients underwent transoral laser microsurgery (TLM) with neck dissection and adjuvant therapy as indicated. The patients had a minimum follow-up of 12 months. The authors used Cox proportional hazard regression analyses to identify variables prognostic for disease-free survival. Patients received level II-IV unless there was concern for level IB based on radiography or physical examination. Patients with tongue base or tonsil tumors approaching or extending past midline and patients with N2c disease received contralateral elective selective neck dissections.

Adjuvant treatment was indicated based on extracapsular spread, multiple or contralateral lymph nodes, and/or positive margins. After 2004, Cisplatin was added to treatments for high-risk cases. High-
risk features included positive margins, multiple metastatic nodes or extracapsular spread (ECS). Adjuvant radiation therapy was given at 60 Gy in 30 fractions unless high-risk features were identified. Elective radiation therapy is given to the contralateral neck at a dose of 52 to 54 Gy. Adjuvant radiation was spared to the primary site if the tumor was a low stage (I-II) or negative margins were achieved on resection. If the patient had a pathologic-negative contralateral neck or were low risk for disease in the contralateral neck, the ipsilateral neck was radiated alone.

The authors examined a total of 171 patients with a median follow-up of 47 months. The three-year Kaplan-Meier estimates for disease-free survival and disease-specific survival where 91% and 95.5% respectively. At 5 years, the estimates were 88% and 94.4% respectively. In their patient population, there was a total of 12 recurrences. Of that, 2 recurrences were local, 4 were regional, and 6 were distant recurrences. There was a disease-free survival difference between smokers and non-smokers. Also, DFS was statistically different between clinical T staging between T3/4 to T1/2. Pathological T staging was also statistically different. Nodal disease was statistically significant when comparing nodal disease. Disease-free survival differences were noted in clinical T stage differences, pathological T stage differences and presence of angioinvasion.

Poor prognostic factors for disease-free survival included cT4 tonsil primary tumors, ever smoking status, 3+ metastatic nodes, pathologic N2b+ staging, and radiation-based adjuvant therapy. Angioinvasion and advanced T staging were poor prognostic factors for disease-specific survival. In evaluating disease-specific survival, the study failed to show a difference with smoking status. Extracapsular extension, nodal stage and margins were not found to be poor prognostic factors. The authors found that surgery was able to give a more accurate assessment of pathological staging rather than relying on clinical stage. A total of 45% of patients with a clinical T4 stage were down-staged in their study. Very few of their patient’s initial clinical stage was upstaged after pathological assessment. However, clinical nodal status was upstages in up to 50% of patients with N1 disease, 25% in N2a disease, and 11% in N2b disease.

When the authors compared their 3 year Kaplan-meier disease-free survival curves to nonsurgical cohorts, they found an improved rate of 91% compared to 74%, 81%, and 87% in HPV-positive OPSCC. Only 7 of the 171 patients died of disease during the study. Using the data collated, a risk stratification table was made. Patient were stratified into three groups (low/high/unknown) based on disease-free survival status. Only patients with clinical T3/4 primaries and angioinvasion based on pathology were considered high risk. (Haughey and Sinha)

**Functional Outcomes of TORS**

As it is well-known, patients must deal with both acute and late toxicities associated with concomitant chemotherapy and radiation. Often, patients require a PEG tube and/or tracheostomy tube during and after treatment. Most studies have looked at comparing both survival differences and functional outcomes between standard chemotherapy and radiation versus TORS. Most studies have found an improved outcome in regards to function. A large comparison of TORS showed tracheostomy tube rates of 0-13%. The study with 31% of patients had all decannulated based on stage at the end of the study. Gastrostomy tube outcomes in related TORS studies was between 0 to 100%. The study with 100%
gastrostomy tube outcome placed gastrostomy tubes in all patients. Other studies were between 0 to 18%. (de Almeida and Genden)

Patient-perceived functional outcomes were evaluated by Sinclair et al utilizing the MDADI questionnaire. The prospective study looked at 42 patients with T1 or T2 OPSCC. 76% of the patients had Stage III disease. 93% of the patients underwent staged neck dissection. Each patient filled out a pre-operative MDADI, an immediate post-operative MDADI and a MDADI at the last follow-up. Dysphagia after organ preservation therapy is affected by radiation doses received to the pharyngeal constrictor muscles. TORS has been able to deintensify post-operative radiation. In the study, 31% of patients received post-operative chemotherapy while comparing standard protocol, a total of 76% of the patients would have received concomitant chemotherapy. This related to a total of 45% of the patients avoiding chemotherapy. Post-operative chemotherapy has been shown to be the only factor predictive of PEG tube retention after 3 months. (Sinclair, McColloch and Carroll)

Sinha et al evaluated 152 patients with p16 disease. They then evaluated extracapsular spread on 2 systems. ECS report was based on any ECS found on pathologic examination. ECS graded was then used as system to grade the amount of ECS on examination. Patients were matched based on multiple parameters. The primary end-points of the study were disease-free survival and recurrence. The median follow-up of the study was 43 months. Patients with ECS were given chemotherapy as adjuvant treatment. ECS was not associated with a poor DFS or with other end points. Further analysis revealed no improved disease-free survival using chemotherapy with adjuvant radiotherapy. (Haughey and Sinha)

**Reconstruction**

Almeida et al reviewed their experience with TORS reconstruction. They formed a 4 class system to classify defects in over 92 patients. The classification system was based on anatomical features affecting complications or functional outcomes. These included the site of the defect, the number of subsites involved, whether there was exposure of the internal carotid artery in the pharynx, communication with the oropharynx and neck during concomitant neck dissection, and more than 50% soft palate resection. Class I defects were classified as only one subsite involved with no adverse features. Class II defects involved more than 1 subsite without adverse features. Class III features involved only one subsite with adverse features. Class IV defects had multiple subsites involved with at least 1 adverse feature.

The algorithm for reconstruction recommended secondary healing with most class I and class III defects. Local flaps were recommended in class II and some class III defects. Most class IV defects were closed with regional or free flap reconstruction. The loss of more than 50% of the soft palate resulted in VPI, hypernasal speech, and reduced speech intelligibility. Many of these defects were closed with superior constrictor advancement flaps. Often, larger defects required closure with radial forearm free flaps. Obviously, exposure of the internal carotid artery or communication between the oropharynx and neck need closure to avoid complications. (de Almedia, Park and Villanueva)

**Current Thoughts**

HPV-positive OPSCC has been shown to improve prognosis regardless of treatment. Surgical treatment of these cancers has lead to equal or improved survival benefits with improved functional
outcomes. There does appear to be a subset of HPV-positive OPSCC with a possible poorer prognosis. Often, these patients have associated tobacco exposure. Questions remain including whether HPV-associated OPSCC should re-stratify and change current treatments. Is there an improved outcome in patients with intermediate risk patients?

**The Future**

Studies continue to show the improved survival in HPV-positive OPSCC. This necessitates a reduction in treatment-related toxicities by reducing treatments. Multiple studies are being performed. Mehrotra et al are performing a Phase III trial looking at reduced radiation doses in non-smoking HPV-positive OPSCC. Patients received induction TPF and those with complete or partial response receive reduced radiation doses. ECOG 1308 is currently evaluating HPV-positive patients with Stage III/IV disease. The patients are receiving induction TPC with cetuximab. Those with a complete response will receive reduced XRT and cetuximab.

Also, studies are examining the effectiveness of reduced toxicity from chemotherapy. The De-ESCALaTE HPV trial is currently looking at comparing standard concurrent chemotherapy versus radiation with cetuximab. The RTOG 1016 is evaluating HPV-positive OPSCC. Patients in this trial are receiving accelerated IMRT with 70 Gy with cisplatin versus accelerated IMRT with 70 Gy and Cetuximab. The ORATOR study is a prospective Phase II trial evaluating quality of life as the primary end-point. Patients in the trial have T1/2 staging, N0-2 nodal stage, nodal size less than 3 cm, and no ECS based on imaging. N0 disease patients will received adjuvant radiation. Patients with N1-2 disease will received concurrent chemotherapy. This study will lead to design of a larger comparative Phase III trial assessing survival. (Kofler, Laban and Busch)

**Conclusions**

Trans-oral robotic surgery is a safe and effective treatment alternative to concurrent chemotherapy and radiation. It has been shown to be as effective if not improved to organ preservation therapy. The epidemic of HPV-related OPSCC has led to a new patient population. These patients are now younger and healthier. Late toxicities can be debilitating to patients especially as the younger patients live longer lives. Many of these toxicities can be avoided. Regardless of the primary treatment option, de-intensifying the treatment will be the likely future of HPV-related OPSCC.

**Bibliography**


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